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Dissecting the Intrastriatal Neuronal Circuitry that regulates Direct and Indirect Striatal Projections

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ABSTRACT

The basal ganglia (BG) are a group of subcortical nuclei that are interconnected in multiple parallel cortico-BG-thalamocortical loops. They have been implicated in many functions, among them action control and motor learning. The striatum forms the main input nucleus of the BG. Its principal neuron type, the medium spiny neuron (MSN), projects via striatonigral (direct) and striatopallidal (indirect) BG pathways, which according to an influential model function antagonistically in motor control. D1 and D2 receptor expressing MSNs ascribed to direct and indirect pathways, respectively, are not easily discriminable based on electrophysiological properties, but are hypothesized to be oppositely affected by dopamine (DA). A small population of striatal neurons, the fast-spiking interneurons (FSNs) however show characteristic stuttering discharge *in vitro*, and have an important role in mediating feedforward inhibition onto MSNs (which are also interconnected via feedback collaterals). FSNs form electrical, as well as chemical synapses onto each other. The focus of this thesis has been to investigate the characteristic electrical properties of the mentioned striatal neuron types and their dynamic interconnectivity, as well as DAergic modulation of MSNs of the different projection systems.

In two animal models (rat and mouse), electrical properties of different MSN subtypes were similar, however, membrane excitability consistently differed with direct pathway MSNs being less excitable than their counterparts. DA had opposite effects on excitability of D1 and D2 MSNs, counteracting these initial differences. Excitability increased in D1 MSNs, across experimental conditions and parameters, and also when applying DA or D1 agonist during blockade of cholinergic, GABAergic, and glutamatergic synaptic transmission.

FSNs provided a strong and homogeneously depressing "feedforward" inhibition of both striatonigral and striatopallidal MSNs, as measured with multineuron patch-clamp recordings in the acute slice. Individual FSNs were connected to MSNs of both types. In contrast, both MSN types received sparse and variable, depressing and facilitating synaptic "feedback" transmission from other MSNs. Connection probability appeared higher for pairs with presynaptic striatopallidal MSNs; however, the type of interconnected MSNs did not determine the variability in synaptic dynamics. The differences between feedback and feedforward inhibitory pathways were clear in two species at different developmental stages.

Measurements *in vitro* and a computational FSN-model showed that FSNs that exhibit typical random stuttering discharge in response to steady depolarization do not show stuttering when they receive fluctuating input. The model predicts that electrically coupled FSNs show substantial spike synchronization only when in the stuttering regime. In vivo variability in FSN discharge was furthermore translated to high variability in postsynaptic amplitudes due to strong depression of the FS-MSN synapse.

Using PV-Cre mice injected with AAV virus containing ChR2 and mCherry, we selectively photostimulated FSNs. When recording from nearby MSNs, FS, low-threshold spiking (LTS), and cholinergic (ACh) interneurons while activating FSNs, most MSNs received strong and reliable synaptic input, which was mediated by GABAa receptors, whereas ACh (and LTS) interneurons received no input at all.

In conclusion, DA induced changes in excitability of identified MSNs were consistent with an influential model of BG function, and direct pathway excitability increases were mediated by D1 receptors most probably acting on intrinsic MSN properties. Synaptic dynamics generally differed between striatal feedforward versus feedback synapses, but were similar for both output pathways. Modeling suggested that *in vivo*, neighboring FSNs are not readily in the stuttering regime simultaneously, discharge variability is rather determined by input fluctuations, and synaptic dynamics lead to highly variable postsynaptic response amplitudes in MSNs. Feed-forward inhibition mediated by FSNs is highly target selective for MSNs in contrast to other interneuron types, especially ACh interneurons.

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